REMARKS

Claims 1-20 have been rejected under 35 U.S.C. 103(a) as being obvious by Li *et al.*, U.S. Patent No. 5,977,163 and in view of Li, *et al.*, U.S. Patent No. 6,262,107 (hereinafter, the '163 and '107 patents, or collectively, the "*Li* patents").

The Patent Office alleges that the *Li* patents teach compositions of paclitaxel formed by conjugating paclitaxel to a polymer such as poly-1-glumatic acid, and combining a paclitaxel conjugate with a platinum drug, methods for making polymer conjugates of other therapeutic agents, and combining a paclitaxel conjugate with other drugs that are used in combination with Taxol.

In the view of the Office, claims 1-20 would have been obvious in view of the *Li* patents because one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The reasoning is that the *Li* patents disclose that the paclitaxel conjugate may be combined with a platinum drug or other drugs that are used in combination with Taxol. Applicant respectfully traverses the rejections.

Pursuant to the response to the election of species requirement, claims 1-12 are being examined to the extent that they read on the elected species of additional chemotherapeutic agent, namely vinorelbine. Claims 13-20 on the other hand, require administration of carboplatin or cisplatin, with claim 15 additionally including vinorelbine.

With respect to claims 1-12 and 15, neither of the *Li* patents explicitly discloses or suggests vinorelbine. A *prima facie* case of obviousness must include a "prior art reference (or references when combined) [that] teaches or suggests all the claim limitations." M.P.E.P. § 2142. Moreover, the Patent Office's contention that the *Li* patents teach the conjugation of other therapeutic agents to polymers is irrelevant since none of

the claims in the present application require a vinorelbine-polymer conjugate.

The lack of *prima facie* obviousness aside, Applicant submits herein that treating cancer patients with a combination of vinorelbine and unconjugated Taxol resulted in increased neurotoxicity. Parimoo, *et al.*, *J. Nat'l. Can. Instit.*, *88*(15):1079-1080 (1996) (copy enclosed). To the extent that the *Li* patents suggest combining conjugated paclitaxel with "other drugs that are used in combination with [unconjugated] Taxol," in view of Parimoo, Applicant submits that one of skill in the art would not have been motivated, at the time the claimed invention was made, to treat a cancer patient with a combination of vinorelbine and conjugated paclitaxel.

Similarly, with respect to claims 13, 14 and 16-20, the *Li* patents do not explicitly teach or suggest carboplatin or cisplatin. Thus, here again *prima facie* obviousness has not been established.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone Applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge

Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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Severe Neurotoxicity From Vinorelbine–Paclitaxel Combinations

A recent report (*1*) indicated enhanced antitumor effects of vinorelbine against murine P388 leukemia when that drug was combined with paclitaxel (Taxol). However, before promoting widespread clinical exploration of the use of these drugs for combination chemotherapy for cancer, we caution that, under some circumstances, this drug combination has the potential to cause severe neurotoxic effects in patients.

Five patients (Table 1) were given a combination of vinorelbine and paclitaxel every other week. After premedication with intravenous dexamethasone, diphenhydramine, and cimetidine, vinorelbine was given intravenously at a dose of 20-30 mg/m^2 over 30 minutes, followed by a 3-hour intravenous infusion of paclitaxel at a dose of 150 mg/m^2. All patients had been pretreated with paclitaxel and carboplatin, and one patient, in addition, was also pretreated with cisplatin. Three of five patients were experiencing stable grade 1 (*2*) sensory neuropathy at the time they began receiving the paclitaxel–vinorelbine combination, while the remaining two exhibited similar but slightly worse neuropathy, classified as grade 2 (*2*), because they required treatment with analgesics. The three patients with ovarian cancer showed decreasing serum levels of CA-125 marker but had to discontinue therapy because of neurotoxic effects. The other two patients (diagnosed with bronchoalveolar carcinoma and tonsillar cancer) also had no progression of their cancer during treatment. All five patients showed some neurologic improvement after the cessation of paclitaxel/vinorelbine administration.

Vinorelbine tartrate and the taxanes, which are mitotic inhibitors with differing mechanisms and tubulin-binding sites, have shown efficacy against ovarian, breast, non-small-cell lung, and head and neck cancers (*3-6*). Preclinical (*1,7,8*) and clinical (*9-11*) studies support their use in combination with the other. Overlapping toxic effects were not viewed as a deterrent to the use of vinorelbine in combination with other drugs that might cause myelosuppression, since cytokine support might be able to overcome neutropenia. In fact, a pilot study of vinorelbine plus paclitaxel in nine patients with metastatic breast cancer (*9*) reported grade 3 or 4 neutropenia (*2*) in all patients and grade 1 or 2 (*2*) peripheral neuropathy in four. However, a larger study (Hortobagyi G: personal communication) from The University of Texas M. D. Anderson Cancer Center, Houston, reported dose-limiting neurotoxic effects and pelvic pain. Furthermore, Hortobagyi subsequently documented vocal cord paresis and severe motor neuropathy. Another study by Kourousis et al. (*10*), using a combination of vinorelbine and paclitaxel together with cisplatin, reported that the patients experienced severe neurotoxic effects. Conversely, a study by Fumoleau et al. (*11*), using combinations of docetaxel and vinorelbine, reported fewer neurotoxic effects than those reported by the Kourousis et al. study.

In patients enrolled in the present study who showed pre-existing sensory neuropathies as a result of earlier treatment with paclitaxel (*12*), there was onset of severe, relentless, and very slowly reversible motor neuropathy following treatment with vinorelbine plus paclitaxel. All five patients manifested

Table 1. Case histories of paclitaxel–vinorelbine-treated patients

Patient age and sex/diagnosis	Prior chemotherapy*	Base-line neuropathy†	Paclitaxel/vinorelbine dose/ mg/m^2/course	Outcome/ neurotoxicity†
52-y-old female/ ovarian cancer	Carbo + paclitaxel, 175 mg/m^2 × 6; DoXIL, 50 mg/m^2 × 7	Grade 1 sensory	Paclitaxel, 150/every 2 wks × 4; vinorelbine, 20/every 2 wks × 4	Stable/grade 3 sensory: hoarseness
75-y-old female/ ovarian cancer	Carbo + paclitaxel, 135 mg/m^2 (24 h) × 6; paclitaxel, 135 mg/m^2 × 3; DoXIL, 40 mg/m^2 × 3; paclitaxel, 200 mg/m^2 + EMP (900 mg/m^2 × 3 d) × 8	Grade 2 sensory	Paclitaxel, 150/every 2 wks × 5; vinorelbine, 25/every 2 wks × 5	Stable/grade 3 sensory; grade 3 motor
68-y-old female/ ovarian cancer	Cisplatin, 50 mg/m^2 + doxorubicin, 50 mg/m^2 + cyclophosphamide, 500 mg/m^2 × 6; carbo + cyclophosphamide, 600 mg/m^2, paclitaxel, 175 mg/m^2 + carbo × 6; paclitaxel, 175 mg/m^2 × 3; paclitaxel, 225 mg/m^2 + EMP (900 mg/m^2 × 3 d) × 6	Grade 1 sensory	Paclitaxel, 150/every 2 wks × 3; vinorelbine, 25/every 2 wks × 3	Negative computed tomograph scan/pelvic pain, slurred speech, paralytic ileus; grade 1 sensory
72-y-old female/ bronchioalveolar carcinoma	Paclitaxel, 225 mg/m^2 every 2 wks × 6; paclitaxel, 200 mg/m^2 + EMP (900 mg/m^2 × 3 d) × 4; paclitaxel, 225 mg/m^2 + carbo × 3	Grade 1 sensory	Paclitaxel, 150/every 2 wks × 2; vinorelbine, 30/every 2 wks × 2	Stable/grade 3 sensory; grade 2 motor
77-y-old male/ tonsillar cancer	Cyclophosphamide, methotrexate, doxorubicin (doses unknown over 2 years); DoXIL, 40 mg/m^2 × 12; paclitaxel, 200 mg/m^2 every 2 wks × 3; paclitaxel, 150 mg/m^2 + carbo × 4	Grade 2 sensory	Paclitaxel, 150/every 2 wks × 2 vinorelbine, 25/every 2 wks × 2	Stable/grade 3 sensory; grade 4 motor

*Carbo = carboplatin, DoXIL = Stealth liposomal doxorubicin, Sequus Pharmaceuticals, Inc., EMP = estramustine phosphate. All paclitaxel regimens were given every 3 weeks and as a 3-hour infusion unless specified. All carboplatin was given with AUC 5 dosing (Calvert formula).
†National Cancer Institute Common Toxicities Criteria.

generalized weakness, and four of the five required a wheelchair. Two of the patients had near total paresis of the toe flexors and extensors. Since vinorelbine causes only mild neurotoxic effects, even when used in combination with cisplatin (*6*), the current data suggest that progression to severe axonopathy and ganglionopathy results when vinorelbine is combined with paclitaxel in patients with pre-existing damage (*13,14*). Moreover, paclitaxel administration by short infusion accentuates sensory neuropathy in a dose-dependent manner (*15*). This drug delivery schedule has led to more severe neuropathy, when used in combination with cisplatin for treatment of patients with ovarian cancer (*16*) than was originally reported in studies using a 24-hour infusion schedule (*17*). Four of the patients in our study had also been treated with estramustine phosphate to enhance paclitaxel action (*18*), but the addition of this drug did not appear to enhance neurotoxic effects in this or other trials.

The use of drug combinations that include taxanes, vinca alkaloids, and/or platinum compounds is becoming more common. The administered drug doses may be further intensified when combined with cytokine usage. It is therefore imperative that clinicians be aware of possible factors contributing to neurotoxic effects of this therapy. We note that a previous report by Dittrich et al. (*14*) has already brought attention to the need for excluding patients with paclitaxel-induced neurotoxic effects from further treatment with vinorelbine. The current data re-emphasize this warning.

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Notes

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Erratum: "Bioregulators Come of Age in the Control of Tumor Growth and Metastasis," by Nicolson [J Natl Cancer Inst 1996;88:479-80 (Issue 8)]. The correct address for correspondence is Garth L. Nicolson, Ph.D., Department of Tumor Biology (Box 108), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.